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# TREATMENT OF RISK in the Glaucoma Continuum

**CME-CERTIFIED MONOGRAPH**

Release Date: January 2006

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*Jointly sponsored by the University of Medicine & Dentistry of New Jersey (UMDNJ), New Jersey Medical School, Institute of Ophthalmology and Visual Science, UMDNJ-Center for Continuing & Outreach Education, and Impact Communications.*



*This activity is supported by an unrestricted educational grant from Pfizer Ophthalmics.*

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## OVERVIEW

Primary open-angle glaucoma is a significant problem affecting more than 2.2 million people over the age of 40 in the United States alone, and it is estimated that this number will climb as high as 3.4 million by 2040. Ocular hypertension (OHT), the only modifiable risk factor for glaucoma, affects 5 to 8 million people over the age of 40. Since damage to the optic nerve may occur in the absence of detectable visual field abnormalities, it is essential to identify which patients with OHT are most likely to benefit from early intervention. Identification of risk factors may permit more precise estimation of global risk for disease progression. Application of global risk estimates in the clinical treatment of these patients may be useful for determining an appropriate management strategy to minimize optic nerve head damage. This activity is designed to describe the basis for a risk model in glaucoma and explore the potential for application of global risk in clinical treatment.

## TARGET AUDIENCE

This activity is designed for glaucoma specialists and ophthalmologists.

## LEARNING OBJECTIVES

Upon completion of this activity, participants should be better able to

- Review the glaucoma continuum
- Explain the concept of global risk as it applies to treatment decisions in glaucoma
- Examine evidence supporting risk calculations
- Determine an appropriate management approach for best clinical outcomes

## Disclosure Declarations

In accordance with the disclosure policies of UMDNJ and to conform with ACCME and FDA guidelines, all program faculty are required to disclose to the activity participants: 1) the existence of any financial interest or other relationships with the manufacturers of any commercial products/devices, or providers of commercial services, that relate to the content of their presentation/material, or the commercial contributors of this activity, that could be perceived as a real or apparent conflict of interest; and 2) the identification of a commercial product/device that is unlabeled for use or an investigational use of a product/device not yet approved.

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## METHOD OF INSTRUCTION

Participants should read the learning objectives and review the activity in its entirety. After reviewing the material, complete the posttest, which consists of a series of multiple-choice questions.

Upon completing this activity as designed, participants will receive a CME credit letter awarding AMA/PRA category 1 credit. If the posttest, registration, and evaluation materials are completed online, participants will receive an electronic, printable statement of credit immediately after successfully completing the posttest. If sent via mail or fax, participants will receive a statement of credit within 6 weeks. Please see the CME Registration Form and Evaluation section at the end of this monograph for complete instructions.

Estimated time to complete this activity as designed is 2.5 hours.

This activity is intended for healthcare professionals only. There is no fee for this continuing medical education activity.

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The activity was prepared in accordance with the ACCME Essentials.

This activity was reviewed for relevance, accuracy of content, balance of presentation, and time required for participation by Robert D. Fechtner, MD, Jason Gorscak, MD, and Roman Shinder, MD.

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# Global Risk Assessment in Patients With Ocular Hypertension

## Introduction

Approximately 1 in 12 Americans over the age of 40 has intraocular pressure (IOP) above 21 mm Hg.<sup>1</sup> Some of these 10 million individuals will eventually develop glaucoma, and some of those will ultimately go blind from the disease. Treating all patients with ocular hypertension (OHT) is unnecessary and costly, but treating none of the patients with OHT deprives those most at risk for developing glaucoma of therapies proven to reduce the likelihood of its progression. Therefore, the optimal strategy is to treat those at greatest risk of undesirable outcomes, but identifying these high-risk patients remains a clinical challenge.

### The goal of this monograph is to answer 2 fundamental questions:

- Can OHT patients at greatest risk for glaucoma-related visual impairment be identified?
- What implications would this risk assessment have for individualized treatment recommendations?

Glaucoma exists on a continuum, beginning with glaucomatous damage to the first axon of the optic nerve and ending with the loss of the last axon. This monograph will review the glaucoma continuum as a tool to assist the staging of eyes at risk for (or afflicted with) glaucoma. The available tests for assessing structural and functional damage will be described in order to identify a patient's location within the glaucoma continuum. Once a patient has been staged within the continuum, assessing their risk of progressing to significant visual loss in

**“People with glaucoma go blind, and people with ocular hypertension progress to glaucoma and go blind.”**

— Robert D. Fechtner, MD

their lifetime requires an estimation of their rate of progression through it. To accomplish this, the concept of global risk assessment in glaucoma will be introduced, in which multiple risk factors are considered in determining the risk of progressing to functional impairment. Individualized risk assessment for cardiac end points, based on identifiable cardiac risk factors, has been made possible through over

50 years of research, and will be outlined here as a guide for developing recommendations for treatment of glaucoma risk based on individual risk factor analysis. Finally, a glaucoma risk calculator will be introduced as a tool for determining an individual patient's risk of progressing through the glaucoma continuum. This early calculator will analyze identifiable risk factors for the conversion of OHT to glaucoma,

and will provide a quantitative estimate of the individual's risk of developing glaucoma. Such an estimate will assist clinicians in determining who to treat based on individualized (patient-specific) glaucoma risk factors.

## Introduction to the Glaucoma Continuum

### Key points

- Glaucoma presents as a continuum that can progress from undetectable disease to functional impairment.
- Both structural and functional testing are necessary to accurately stage a patient on the continuum.
- Individualized risk assessment may allow a more accurate estimated rate of progression.

Primary open-angle glaucoma (POAG) is a major public health issue in the United States.

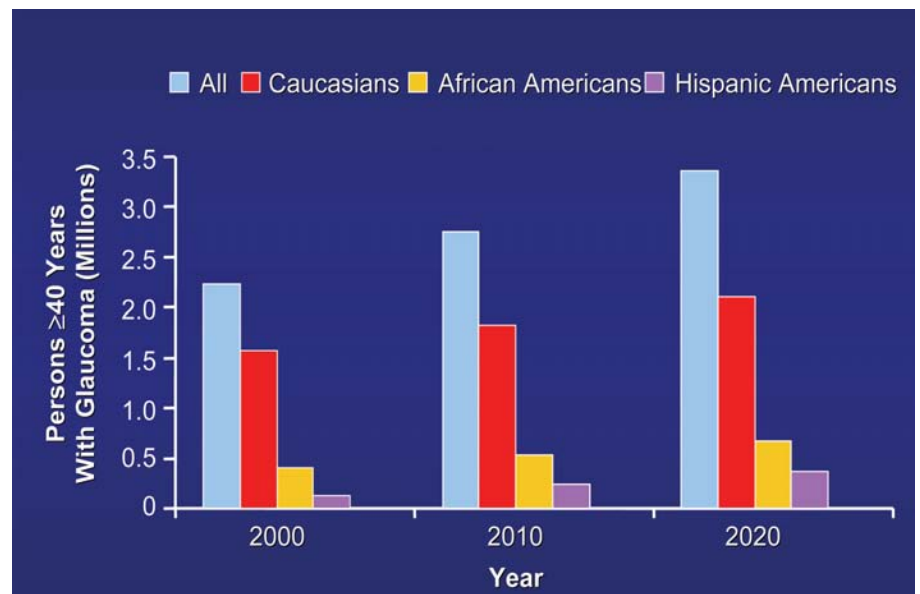


Figure 1. Estimated number of US patients with glaucoma by ethnicity. Adapted from the Eye Diseases Prevalence Research Group. *Arch Ophthalmol.* 2004;122:532-538.

Recently, it has been estimated that 1.9% of Americans over age 40 have glaucoma—which represents over 2.2 million individuals. Given ever-increasing life expectancies arising from medical advances directed against common killers such as cancer and cardiovascular disease, the number of glaucoma patients in the United States is expected to climb to over 3.4 million in the next 15 years.<sup>2</sup>

The American population comprises many different ethnic groups, and the prevalence of glaucoma varies significantly among these groups. For instance, African Americans have a 4- to 5-fold higher risk of developing glaucoma than Caucasians,<sup>3</sup> and Hispanics are at least twice as likely as Caucasians to have glaucoma.<sup>4</sup> In addition to ethnic variations in prevalence, severity of glaucoma also appears to vary among ethnicities, and African Americans are up to 10 times more likely to be blinded by glaucoma than Caucasians. Glaucoma is now the leading cause of blindness for both African Americans<sup>5</sup> and Hispanics<sup>6</sup> in the United States. The number of glaucoma patients is increasing in all ethnic populations (Figure 1), especially among Hispanics, whose numbers in the United States are expected to nearly double in the next 2 decades.<sup>7</sup>

The lack of symptoms at the early stages of glaucoma can hamper the public health effort to prevent glaucoma-related blindness. It has been estimated that approximately half of Americans with glaucoma are undiagnosed and not receiving treatment to prevent blindness.<sup>1</sup> Among Hispanics, up to 75% may be unaware of their disease.<sup>4</sup> Screening efforts to identify affected individuals are hindered by poorly defined criteria for screening failure and low follow-up rates for identified individuals.<sup>8</sup> As a result, newly identified glaucoma patients often

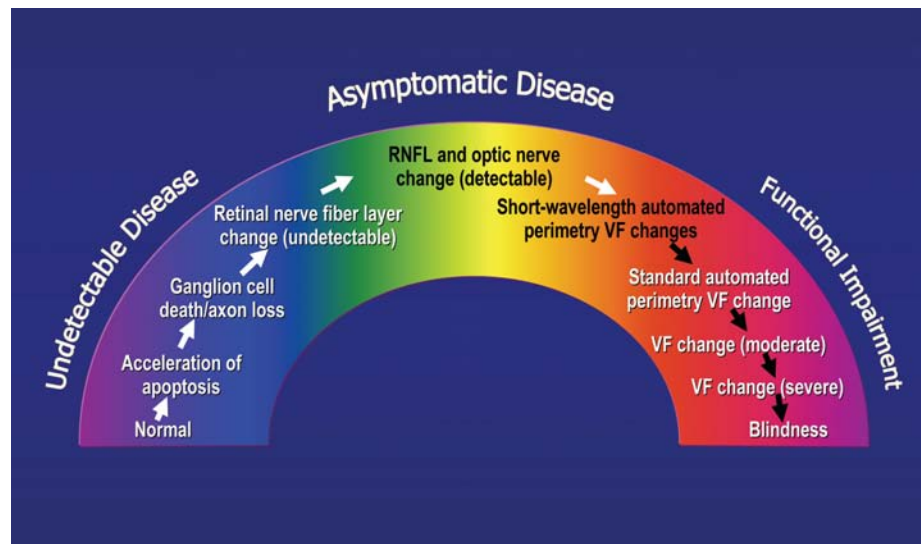


Figure 2. Undetectable disease may progress to functional impairment. Weinreb et al. *Am J Ophthalmol.* 2004;138:458-467.

have significant visual field loss at the time of diagnosis.<sup>9</sup>

The glaucoma continuum (Figure 2) is a useful tool for staging glaucoma based on the structural and functional changes known to occur throughout the disease.<sup>10</sup> The continuum spans the range of glaucoma from undetectable changes within the visual

pathway at one extreme, to severe vision loss and eventual blindness at the other.

Early in the continuum, the eye is structurally and functionally intact. It may or may not have elevated IOP. While it is neither necessary nor sufficient to cause glaucomatous optic neuropathy, elevated IOP is the primary risk factor, as well as the only known modifiable risk factor

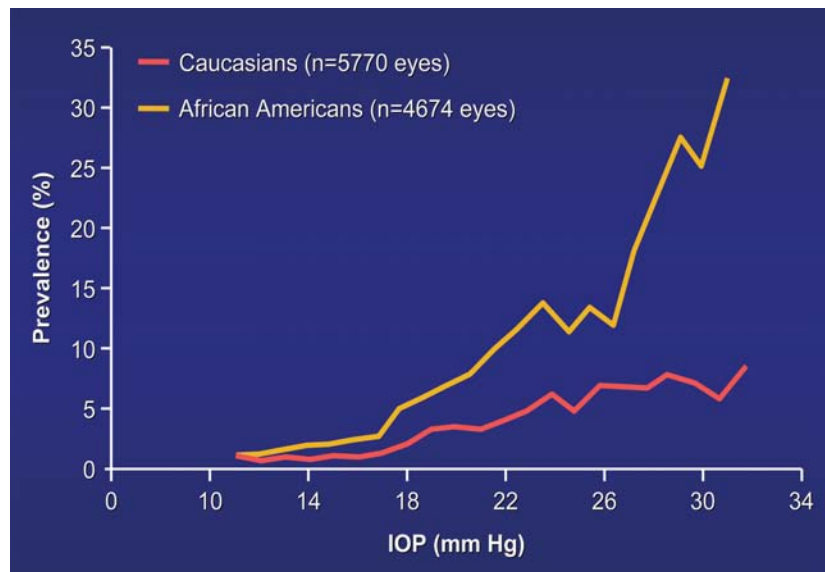


Figure 3. Glaucoma prevalence in African Americans and Caucasians by level of IOP: a continuous incremental relationship (especially in African Americans). Reprinted with permission from Sommer et al. *Arch Ophthalmol.* 1991;109:1090-1095.

for glaucoma. Approximately 7% to 8% of Americans (10 million individuals) have IOP above 21 mm Hg.<sup>1</sup> The Baltimore Eye Survey demonstrated a progressively higher prevalence of glaucoma in eyes with progressively higher IOP (Figure 3). This relationship was particularly strong in African Americans, in whom the prevalence of glaucoma increased sharply as a function of increasing IOP.<sup>1</sup>

There is a slow but steady lifelong loss of retinal ganglion cells (RGCs) and their axons in all eyes, including those that are structurally and functionally intact. Everyone slowly loses reti-

**“We don’t find early glaucoma. We only find glaucoma when it is moderately advanced because that is the earliest our current technology can detect it.”**

— Robert D. Fechtner, MD

nal ganglion cells due to aging via the process of apoptosis, or programmed cell death. What distinguishes normal aging from the onset of glaucoma is the rate of RGC loss: in the continuum, glaucoma begins when an individual’s rate of axonal loss exceeds the normal age-related rate of loss.

This earliest stage of glaucoma is undetectable with current diagnostic tests and is also asymptomatic. Recent studies have demonstrated, however, that even during this undetectable stage of the disease structural changes can occur at all levels of the visual pathway, not just the optic nerve and retinal nerve fiber layer (RNFL). Retinal ganglion cells die through apoptosis,<sup>11</sup> and there also can be permanent changes in the lamina cribrosa early in glaucoma.<sup>12</sup> In the lateral geniculate nucleus, there can be alterations in relay neurons in early glaucoma that can precede any demonstrable loss of retinal ganglion cells.<sup>13</sup> Neuronal death even

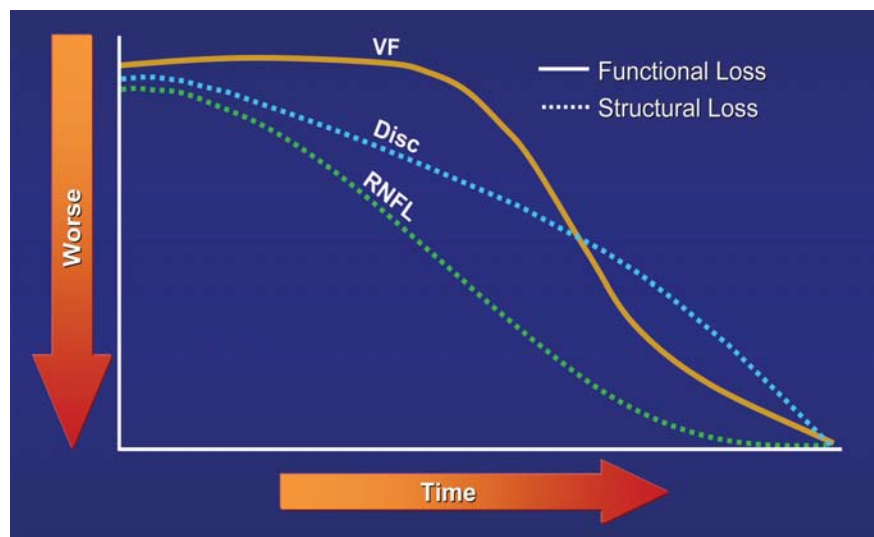


Figure 4. Structural damage may precede functional vision loss. Weinreb. Presented at: The AGS Subspecialty Day Lecture: Getting Closer to Glaucomatous Optic Neuropathy; October 19, 2002; Orlando, Fla.

can be observed in the visual cortex in eyes with early glaucoma.<sup>11</sup>

As glaucoma progresses, the earliest detectable changes in structure and function become manifest with appropriate testing, although patients at this early stage remain asymptomatic. In many eyes with glaucoma, structural changes precede functional deficits (Figure 4).

Commonly, the earliest identifiable structural change detectable in glaucomatous eyes is

focal loss of the RNFL, manifesting as a NFL bundle defect or as focal thinning or notching of the neuroretinal rim. NFL bundle defects can be identified by careful clinical examination using the slit-lamp and a hand-held condensing lens, but are often more readily visible in photographs, either color or red-free (Figure 5).

These early defects may not be associated with detectable defects on standard (white-on-white) automated perimetry (SAP), but sometimes may be demonstrated using more

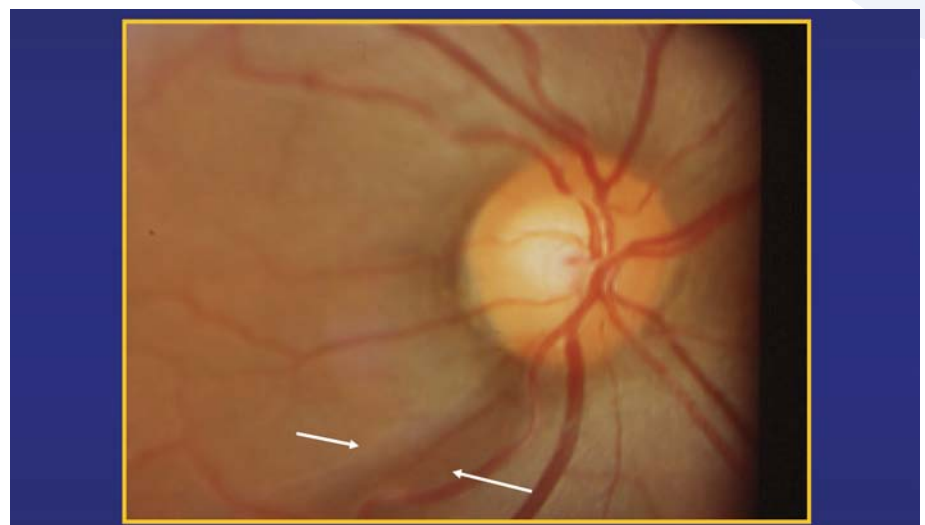


Figure 5. Nerve fiber layer loss. Courtesy of Robert N. Weinreb, MD.

sensitive selective perimetric methods, such as frequency-doubling technology (FDT)<sup>14</sup> or short-wavelength (blue-on-yellow) automated perimetry (SWAP).<sup>15</sup>

With further progression, the optic nerve often exhibits the classic features of glaucomatous optic neuropathy: progressive focal thinning or notching of the rim, vertical elongation of the optic cup arising from loss of rim at both the superior and inferior poles, enlargement of the optic cup from diffuse axonal loss, baring of the vessels coursing through the optic nerve substance, and splinter hemorrhages on or near the disc surface.

Less commonly, functional defects precede detectable structural changes. In a small proportion of glaucomatous eyes, abnormal perimetry can be demonstrated despite no detectable abnormalities of the optic nerve or NFL. This is particularly common in eyes with small optic nerves, where even mild cupping can be mistaken for normal cup–disc topography. Small optic nerves—often described as “crowded”—rarely have significant cups. Clinicians should be suspicious of glaucoma in any eye with a small nerve and even modest cupping.

The glaucoma continuum spans the range from undetectable disease to significant visual impairment. As a clinical tool, the continuum assists physicians in staging the severity of glaucoma in individual patients. Staging requires assessment of both the structural and functional status of the optic nerve, which in turn requires a combination of technology and careful clinical examination. Staging a patient on the glaucoma continuum is the first step in assessing the rate of progression through the continuum, which in turn facilitates estimation of the risk of functional vision loss within the patient’s expected lifetime.

## Assessing the Patient’s Stage in the Disease Continuum

### Key points

- Thorough clinical evaluation of the optic nerve may reveal glaucomatous changes before any visual field loss is apparent on SAP.
- Selective perimetric methods—such as SWAP and FDT perimetry—may demonstrate visual field defects before SAP.
- Each of the commercially available optic nerve and NFL imaging devices has its own strengths and limitations.

Assessment of the structure and function of the optic nerve and peripapillary NFL is fundamental to glaucoma diagnosis and management as the first step in staging a patient on the glaucoma continuum. The American Academy of Ophthalmology’s *Preferred Practice Pattern for Primary Open-Angle Glaucoma* (PPP) recommends that every patient undergo clinical evaluation of the optic nerve, NFL, and visual field in order to detect glaucoma and its progression.<sup>16</sup> Detecting progression requires identifying change over time, so documenting the status of the optic nerve at regular intervals is critically important. The PPP also recommends graphical documentation of the optic nerve’s appearance—whether by a sketch of the nerve or by optic disc photography—at the time of initial diagnosis and at regular periodic follow-up intervals in order to optimize the ability to detect progression over time.

In real-world clinical practice, however, these recommendations are followed in suboptimal fashion. Fremont and colleagues recently conducted a nationwide, retrospective review of charts of newly diagnosed glaucoma patients.<sup>17</sup> In the period of time from 1 year before the

diagnosis of glaucoma to 6 months after the diagnosis, more than 90% of patients had documentation of visual acuity, IOP measurement, and clinical examination of the optic nerve, but only half (53%) had graphical documentation (either a drawing or photograph) of the nerve’s appearance for subsequent comparisons. In addition, one third of patients (34%) had not undergone formal visual field testing. Without visual field testing and optic nerve evaluation, detecting progression is essentially impossible.

These data are not isolated findings. Coleman and colleagues have studied the frequency with which visual field testing is performed before glaucoma surgery.<sup>18</sup> In their Medicare population, they discovered that one third (33%) of patients undergoing trabeculectomy did not have a visual field test within the year before the surgery.<sup>18</sup> A comparable number (36%) had no visual field test in the year preceding combined cataract and glaucoma surgery.

Examining a Medicare database, Friedman found that only 6% of patients had documentation of optic disc appearance every 18 months. Thus, progression in these patients could not be determined based on a change

**“If you rely on visual field testing alone, you will often diagnose glaucoma late.”**

— Robert N. Weinreb, MD

in the appearance of the optic nerve. In the same study, fewer than one third (31%) of patients underwent visual field testing every 18 months, precluding detection of progression based on worsening visual fields.<sup>19</sup> In fact, Friedman reported that nearly one fifth (18%) of treated glaucoma patients didn’t even have office visits on an 18-month basis, clearly preventing detection of disease progression by any means. Although the basis for these disconcerting data is not known, the introduction into clinical practice of innovative ways to

document the functional and structural status of the optic nerve provides the promise of earlier diagnosis and detection of progression.

The development of automated perimetry revolutionized visual field testing, and SAP has become the usual method of visual field assessment in glaucoma. Using the familiar bright white stimulus against a lighter white background (white-on-white), SAP is nearly universally available, relatively easy for experienced test subjects to perform, and identifies visual field loss in moderate and advanced glaucoma well. Statistical software transforms the raw data into an evaluable form, and software to detect progression of the visual field over time is also available. The recent development of the Swedish Interactive Thresholding Algorithm (SITA) test strategy, which uses information acquired during a given test to maximize efficiency in completing the test, has trimmed substantial time off the testing process, permitting full threshold testing on the order of 5 minutes per eye. In essence, SITA applies patient responses in individual test locations to neighboring test locations, which is valid because scotomata edges are generally

gradual rather than steep, and normal test points are unlikely to lie adjacent to severely damaged test points.

But, despite its many advantages over manual kinetic perimetry, SAP does have limitations. Intertest variability is high, and can often mimic field progression. In the Ocular Hypertension Treatment Study (OHTS), patients with OHT and normal SAP were followed with SAP every 6 months for 5 or more years. Of the patients who manifested a new glaucoma defect on one of the follow-up fields, 86% reverted back to normal on retesting.<sup>20</sup> Interestingly, patients who manifested a new field defect on 2 consecutive tests (a new defect confirmed with a second test) reverted back to normal on the third test 50% of the time. This high degree of variability underscores the need for multiple tests to confirm a new defect or progression of an existing defect, so that patients don't have treatment advanced just because they performed poorly on the test.

Perhaps the most significant limitation of SAP is its relative insensitivity to early glaucoma defects. Up to 25% to 50% of axons can be

lost, but are not always lost, before patients lose the ability to detect the bright white light against the dim white background.<sup>21</sup> In contrast to achromatic perimetry, selective functional testing, such as SWAP and FDT perimetry, can provide enhanced diagnostic sensitivity.

SWAP is similar to SAP, but differs in that there is a blue stimulus and yellow background. SWAP has been shown to detect glaucoma defects as much as 10 years earlier than SAP,<sup>22</sup> and in some patients it also detects progression of existing defects substantially earlier than SAP.<sup>23</sup> SWAP assesses blue-yellow opponency, which is a function of the koniocellular subset of retinal ganglion cells, and now is available on most recent Humphrey Field Analyzers.

SWAP has limitations. Chief among them is high variability—even higher than with SAP. False-positive SWAP tests are even more common than false-positive SAP tests, and all abnormal SWAPs must be confirmed to be assured that observed defects are likely to be real. SWAP is sensitive to other eye diseases, such as cataract and macular degeneration, both of which can produce abnormal test results even in eyes with no visual field loss. Also, the current testing strategy requires a long test time—on the order of 15 minutes per eye; fatigue may explain some of the high variability. SITA-SWAP is now available. Use of this testing paradigm will significantly reduce test time, and may also reduce variability.

FDT is another form of perimetry that can identify eyes with early glaucoma. FDT is based on a psychophysical phenomenon known as the frequency-doubling illusion: when a pattern of black and white stripes of appropriate width is rapidly interchanged with an identical pattern of white and black stripes, the intact human visual system perceives the width of the stripes to be halved and the number of stripes to be doubled (Figure 6).

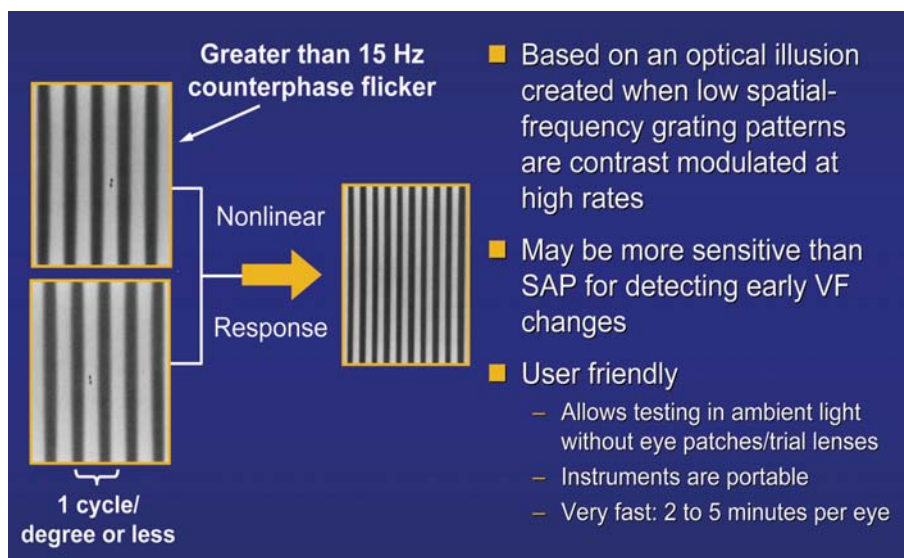


Figure 6. FDT may detect early damage. Adapted from Johnson et al. *Invest Ophthalmol Vis Sci.* 1997;38:413-425; Medeiros et al. *Am J Ophthalmol.* 2004;137:863-871.

This frequency-doubling illusion is mediated by a subset of magnocellular retinal ganglion cells.<sup>24</sup> If the doubling effect is not perceived (ie, if the magnocellular pathway is damaged), the rapid alternation of black and white stripes appears as a gray patch as the visual system “averages” the 2 rapidly alternating colors. Thus, if the FDT stimulus is shown in different regions of the visual field against a gray background (the same color as the “averaged” gray), intact regions of the retina should detect the stimulus pattern and damaged retinal regions will not.

There are 2 commercially available FDT perimeters: the original FDT perimeter and the new Matrix device. The major difference between them is that the original device only tests 17 retinal locations—4 per quadrant and a center spot—while the new device has higher resolution and can perform a standard 24-2 testing pattern. In numerous studies, FDT perimetry has demonstrated high sensitivity and specificity for detecting glaucoma at all stages, and may be more sensitive than SAP in detecting early visual field defects.<sup>14</sup>

The devices have several important attributes. They are lightweight and portable, can be used in ambient lighting, and do not require spectacle correction, obviating the need for trial lenses or eye patches. These features position the FDT devices as potentially useful screening tools.

FDT perimetry also has limitations. The existing normative database is small and may not represent the breadth of the glaucoma continuum. Also, the technology is new, and lacks long-term follow-up data, limiting its applicability in detecting progression of existing defects over time. The advantage of a rapid testing time with the original FDT device is lost with the Matrix device that tests so many more locations. In addition, FDT perimetry is also sensitive to nonglaucomatous conditions, including cataract<sup>25</sup> and diabetes.<sup>26</sup>

- Assess disc size
- Evaluate neuroretinal rim (ISNT)
- Disc hemorrhage
- RNFL

Figure 7. Clinical examination of optic disc.

In concert with functional measures of optic nerve health, assessment of the optic disc and RNFL provides additional information about the overall health and integrity of the retinal ganglion cells and their axons. There are numerous methods for assessing and documenting the optic nerve’s appearance, and each has its particular advantages and limitations.

The most practical method of assessing optic nerve appearance is simply to examine it with a handheld lens and slit lamp biomicroscopy. It is helpful to develop a systematic way of evaluating the optic nerve appearance, one that addresses each of the aspects of the anatomy that are relevant to glaucoma. These include disc size, the neuroretinal rim area, presence of disc hemorrhages, and integrity of the peripapillary NFL (Figure 7).

Disc size is important, in part because glaucoma may not be as apparent in small optic discs as in large discs. Conversely, large optic discs have large scleral canals with physiologically large optic cups that can mimic glaucoma. Disc size can be measured in several ways. The easiest method is with the direct ophthalmoscope. Light projected on the retina through the smallest aperture on the Welch Allyn direct ophthalmoscope illuminates a circle roughly equal to an average-sized optic nerve. Projecting this light on the optic disc thus permits a qualitative assessment, revealing whether a given disc is small, average, or large in size. Quantitative assessment can be performed at the slit-lamp using a handheld condensing lens. Once the vertical slit of light falls on the optic disc, the

height of the slit can be adjusted to equal the height of the disc. The various lenses—60D, 78D, and 90D—all have different magnifying effects, so the measured height should be adjusted for this effect based on the lens used for viewing. A +60D lens has a correction factor of x 1.0, 78D lens x 1.1, and 90D x 1.3.<sup>27</sup>

Inspecting the architecture of the neuroretinal rim will reveal the typical glaucomatous changes described above, including rim thinning or notching, as well as vertical or generalized enlargement of the cup. The inferior, superior, nasal, temporal (ISNT) rule is helpful in assessing neuroretinal rim health: in a healthy optic nerve, the rim should be widest in the inferior quadrant, followed by the superior rim, then the nasal rim, and the temporal rim should be the narrowest quadrant. If the ISNT rule is violated, there is a high probability that the nerve ISNT normal.

The presence of a disc hemorrhage is a risk factor for glaucomatous progression,<sup>28,29</sup> and may serve as a signal to consider whether IOP targets are low enough. Disc hemorrhages can be obvious and unmistakable, but can also be subtle. Hemorrhages may be within the substance of the neural rim, or on its surface, but can also occur in the peripapillary region. In general, hemorrhages within 1 disc diameter of the disc margin are considered disc hemorrhages, although other causes of such hemorrhages—such as diabetic or hypertensive retinopathy, or posterior vitreous detachment—should be excluded. Frequently, disc hemorrhages that were not apparent during the clinical examination can be identified in photographs, underscoring the importance of reviewing such photos before filing them.

The peripapillary NFL is frequently overlooked during examination, largely because it is often difficult to visualize. In young people, the NFL is thick, has a vibrant sheen, and often can be visualized. These features often dissipate with

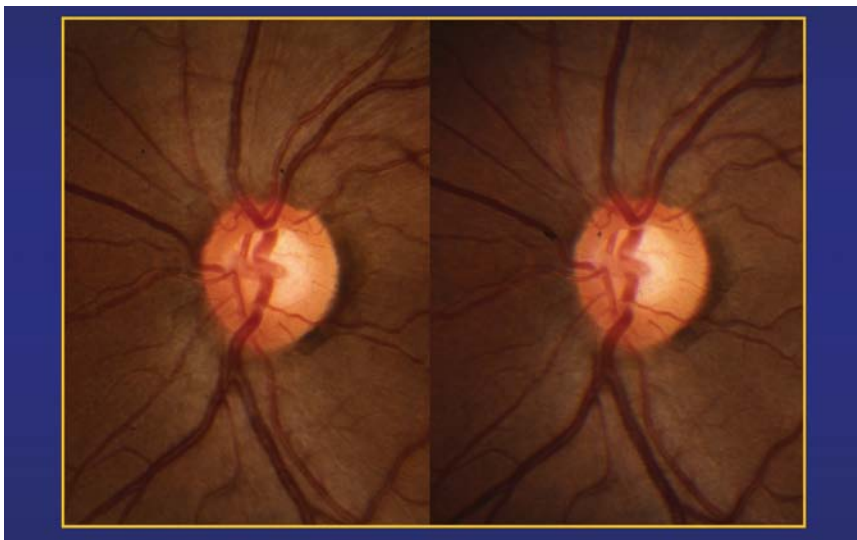


Figure 8. Stereophotography: current standard for structural assessment. Courtesy of C. Girkin, MD, MSPH.

age, particularly in the presence of cataracts. Viewing the posterior pole with red-free light will often enhance the visibility of the NFL, and can facilitate the detection of focal bundle defects. Similarly, red-free photography can enhance detection of NFL defects.

Once examined, the appearance of the optic nerve must be documented in order to detect possible changes later. Simply recording a cup–disc ratio, 0.6 for example, does not provide an adequate level of detail for future comparison. An image of the optic nerve should be recorded in the medical record at each assessment. This can be as simple as a quick sketch, which can capture focal thinning or notching, vertical elongation, and disc hemorrhages. But the gold standard for documenting the nerve’s appearance is photography, specifically stereoscopic photography.

Stereo photography captures a permanent and reproducible record of the status of the optic nerve at any moment in time (Figure 8).<sup>30</sup>

Baseline disc photographs can facilitate detection of later changes, which can be confirmed by repeating and comparing serial photographs. Most importantly, stereo disc photography has

remained a stable platform for decades. Other technologies for assessing and documenting the status of the nerve continue to evolve, and as new iterations of these devices appear, data collected on older models may become inaccessible over time.

Stereo disc photography is not without its challenges. Acquiring useful images requires a skilled photographer. Photographs must be reviewed and interpreted by the ordering dini-

cian. Goals of this review should include an assessment of the quality of the images, assurance that no pertinent findings captured on film were overlooked on examination (such as disc hemorrhages), and the documentation of the review in the medical record. Ideally, images should be stored in the medical record in order to be readily available for comparison at each subsequent visit. An additional limitation of disc photography is its qualitative nature—to date, there are no useful statistical software applications to facilitate quantitative analysis of disc photographs.

Quantitative analysis of optic disc and NFL parameters is possible with a number of imaging modalities. These include confocal scanning laser ophthalmoscopy (CSLO), scanning laser polarimetry (SLP), and optical coherence tomography (OCT).

CSLO technology is the basis for the Heidelberg Retina Tomograph (HRT), which scans sequential axial planes along the optic disc and reconstructs a 3-dimensional topographic map of the disc’s structure from these serial image slices (much like a CT scan) (Figure 9).

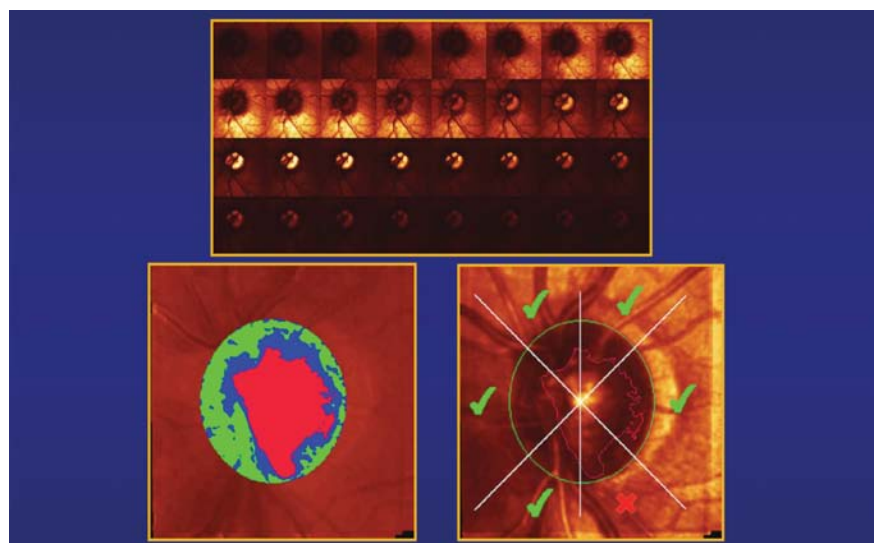


Figure 9. Confocal scanning laser ophthalmoscopy (CSLO-HRT): topographical construction from sequential axial images. Adapted from Heidelberg Engineering, Inc., 2004; Courtesy of Robert N. Weinreb, MD.

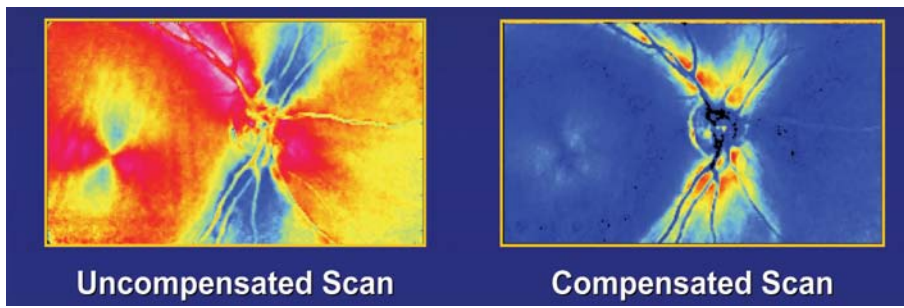


Figure 10. GDxVCC. Zhou and Weinreb. *Invest Ophthalmol Vis Sci.* 2002;43:2221-2228.

In clinical studies, HRT's ability to discriminate glaucomatous optic nerves from normal optic nerves approaches that of examination by a skilled clinician.<sup>31</sup> In addition, a recent study demonstrated that HRT data can predict future glaucoma end points, including change in stereophotographic appearance and visual field loss. A normative ethnic-based database also exists, permitting statistical analysis and detection of deviations from population averages.<sup>32</sup> Also, the HRT data include a measure of disc size. While the HRT provides fast acquisition and retrieval of data in a digital format that facilitates long-term archiving, the technology has some limitations. HRT cannot detect disc pallor or hemorrhages. Moreover, HRT does not account for known IOP-dependent changes in optic disc topography, thus changes detected between scans acquired at different IOP levels may not reflect true progression (or apparent improvement). Until recently, all parameters provided by the HRT have been based on an operator-defined disc margin, requiring a skilled operator. New software automatically defines the optic disc margin, but has not yet been validated.

The GDxVCC is based on the technique of scanning laser polarimetry. Polarized light is slowed as it passes through a birefringent structure such as the NFL. The GDxVCC infers the thickness of the peripapillary NFL by measuring the extent to which incident-polarized light passing into and then back out of the eye is retarded. Since the cornea (and the lens to a lesser extent) is also variably birefringent in individuals, the GDxVCC

has a variable corneal compensator (hence the VCC).<sup>33</sup> This compensator determines the corneal contribution to total retardation by imaging the fovea, where the NFL is not present, and corrects for this corneal birefringence (Figure 10).<sup>34</sup> The GDxVCC often produces atypical scans in elderly eyes,<sup>35</sup> and is poorly reproducible in eyes with macular disease.<sup>36</sup>

Optical coherence tomography provides retinal and NFL thickness measurements derived from cross-sectional retinal images.<sup>37</sup> Widespread use of the Stratus OCT to assess the RNFL has been limited by high cost (relative to other imaging devices), the frequent need for pupillary dilation to obtain quality images, and the need for a highly experienced operator.

Although each of these technologies has demonstrated an ability to distinguish normal

and glaucomatous optic nerves, none has convincingly demonstrated the ability to detect change over time. Of the 3, the CSLO platform has had the most stable hardware and has been most rigorously evaluated for change detection. But at present, clinical examination with a handheld lens and photographs are probably still best for detecting structural changes in the optic disc and RNFL.

There are more tools than ever before to assist in evaluation of the structure and function of the glaucomatous optic nerve (Figure 11).

While these tools provide new and important information, assimilating the various pieces of information into a cohesive assessment of nerve status can be challenging. What combinations of normal and abnormal studies of structure and function represent glaucoma? Glaucoma detection can be generalized as follows<sup>38</sup> (Figure 12):

- 1). A structural defect demonstrable by 2 or more measures of structure (for instance, a disc abnormality with a corresponding NFL defect).
- 2). A structural defect corresponding to a functional defect (for instance, a disc or NFL defect with a corresponding visual field defect).

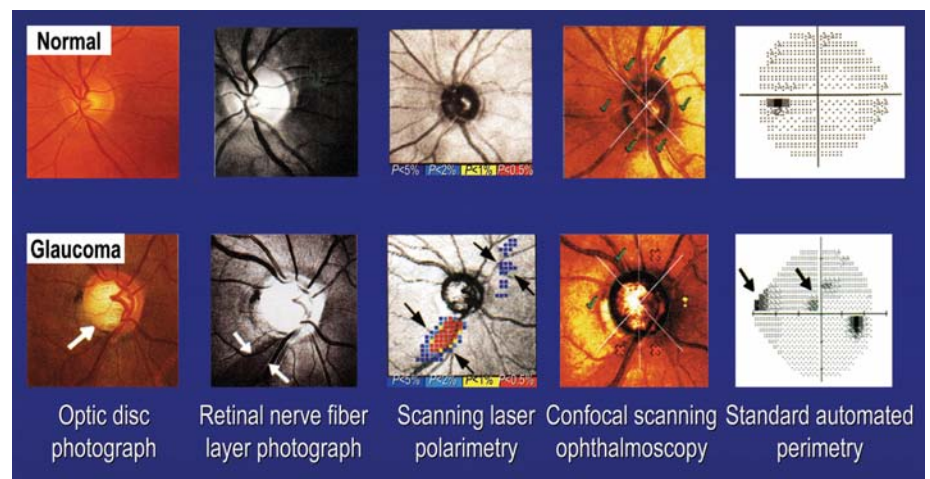


Figure 11. Optic disc assessment. Weinreb et al. *Lancet.* 2004;363:1711-1720.

Abnormal	Normal	Diagnosis	Treatment
NFL,* disc,† and VF‡		Glaucoma	+
NFL and disc	VF	Early glaucoma	+
NFL and VF	Disc	Early glaucoma (typical in small optic discs)	+
VF	Disc and NFL	Possible glaucoma (also look for other causes of VF defect)	Retest VF +/-
NFL	Disc and VF	Possible glaucoma	Other VF testing Wait for progression -
Disc	NFL and VF	Disc anomaly? Possible glaucoma?	Other VF testing Wait for progression -

Figure 12. Glaucoma diagnosis. Courtesy of Robert N. Weinreb, MD. \*NFL—SLP, OCT; †Disc—CSLO; ‡VF—SWAP, FDT.

3). A progressive change in structure or function over time.

### Global Risk Assessment: What Can Be Learned From the Cardiovascular Model?

#### Key points

- Global risk assessment estimates an individual's risk of disease based on multiple risk factors.
- Cardiologists have pioneered the application of global risk assessment and have reduced cardiovascular mortality as a result.
- Cardiovascular disease and glaucoma have important parallels, suggesting that a similar approach to risk assessment may be productive in glaucoma risk assessment.

Glaucoma diagnosis and management are based in part on educated guesses. Is this unusual appearing optic nerve glaucomatous? Is the IOP low enough to prevent further damage? Will this patient become blind in her lifetime? The answers to these questions usually are not known with certainty at the time that they are raised. Instead, best estimates to answer these questions are formulated based on scientific evidence and experience. Estimation of risk is particularly important.

The term *global risk assessment* describes the process by which all of these risk data are assimilated. Global risk assessment estimates a patient's overall risk for the onset and progression of disease based on multiple—rather than single—risk factors. Ideally, global risk assessment applied to individual patients will help guide treatment decisions, leading to optimized patient care.

It is helpful to consider the concept of global risk assessment in the context of cardiovascular medicine, where its application has revolutionized medicine's approach to patients at risk for cardiovascular disease. The quest for a cardiovascular risk calculator began over 50

years ago with the recognition that cardiovascular disease was—and remains—an enormous public health issue. Coronary heart disease is the leading cause of death in the United States, affecting 13 million Americans and accounting for 1 in 5 deaths. Americans have a 50% chance of developing coronary heart disease in their lifetimes. The economic costs associated with coronary heart disease are staggering, with annual costs in the United States estimated at \$142 billion.<sup>39</sup> Glaucoma is also a major public health issue in terms of prevalence, risk of visual impairment, disability, and cost.

It is useful to review the evolution of the modern day cardiovascular risk calculator because it parallels and has preceded the development of a glaucoma risk assessment calculator. Like glaucoma, cardiovascular disease is a chronic disease that arises in individuals who were previously healthy. Also as in glaucoma, cardiovascular disease occurs in a continuum that begins as undetectable disease (early atherosclerosis), progresses to detectable but asymptomatic disease (silent ischemia that may be made manifest with diagnostics such as stress testing or perfusion scans), progresses further to symptomatic end points (angina, acute myocardial infarction), and ultimately leads to permanent damage to heart muscle tissue and end-stage heart disease (Figure 13).

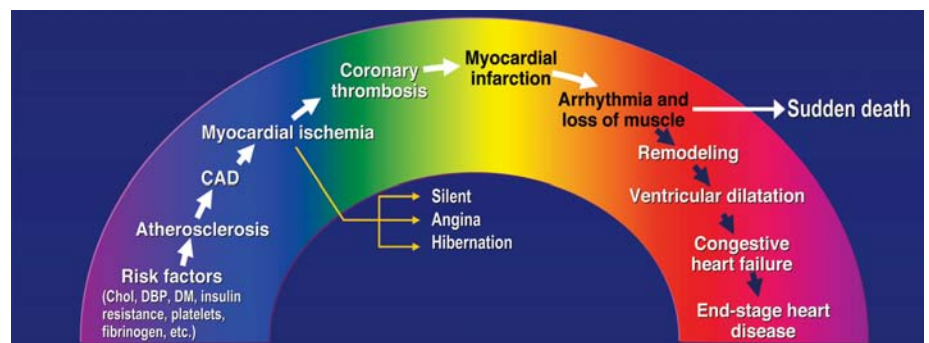


Figure 13. Early treatment may prevent progression. Adapted with permission from Dzau et al. *Am Heart J*. 1991;121:1244-1263. DBP=diastolic blood pressure; DM=diabetes mellitus; CAD=coronary artery disease.

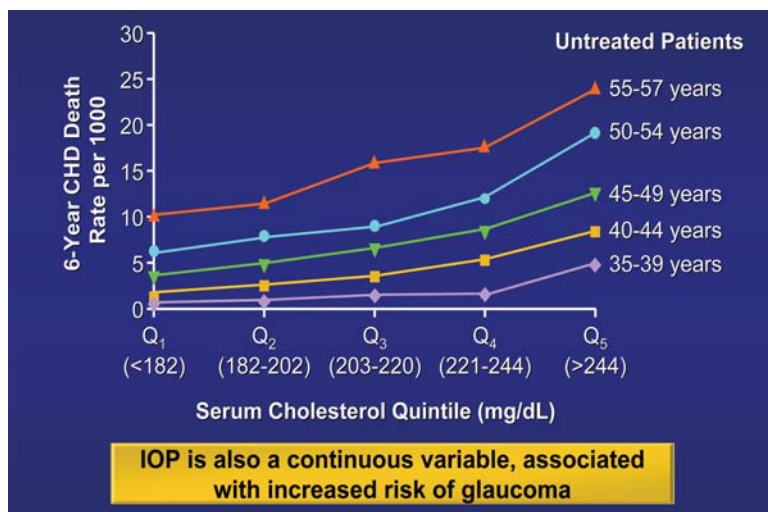


Figure 14. Increasing total cholesterol and age increase risk of CV event: first studies to link cholesterol with CHD mortality (1986). Kannel et al. *Am Heart J.* 1986;112:825-836. Q=serum cholesterol quintile.

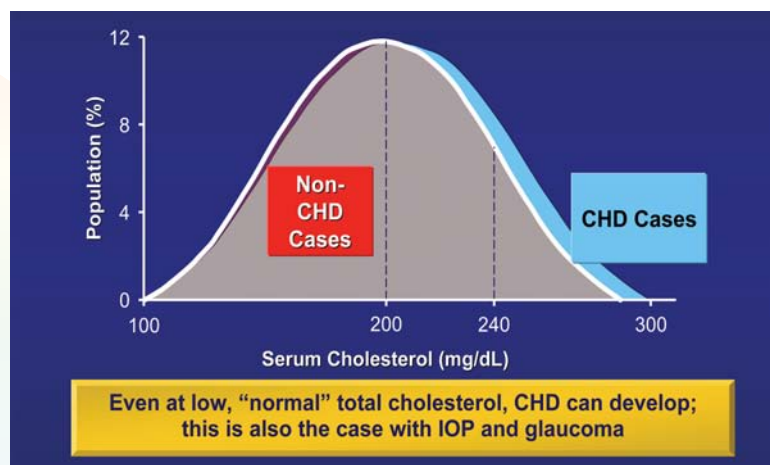


Figure 15. “Abnormality” is difficult to define. There is significant overlap of total cholesterol levels in CHD vs non-CHD cases. Adapted from Kannel et al. *Am Heart J.* 1986;112:825-836.

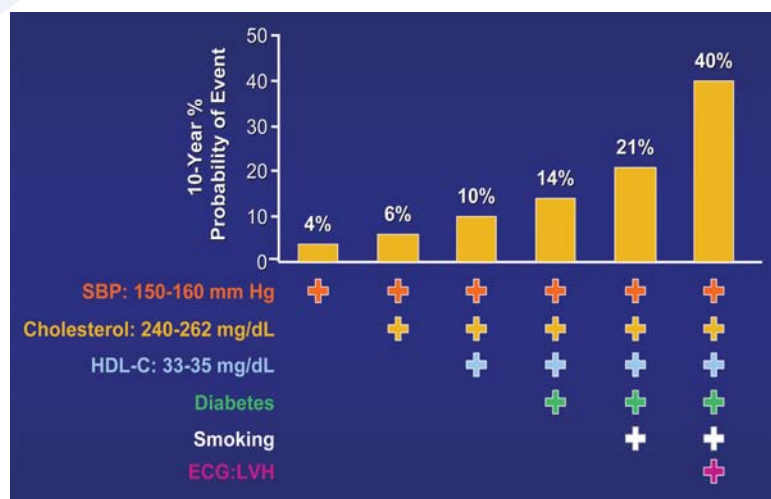


Figure 16. Influence of multiple factors on risk of a CV event. Kannel. *Am J Hypertens.* 2000;13:3S-10S. SBP=systolic blood pressure; HDL-C=high-density lipoprotein cholesterol; ECG:LVH=electrocardiographically verified left-ventricular hypertrophy.

Not only are there similarities in the diseases themselves, but there are also similarities in the treatment strategies for both glaucoma and cardiovascular disease. In neither condition is the disease itself treated (the optic neuropathy or the heart muscle); instead, risk factor modification is the aim of treatment to reduce the risk of developing the disease in the first place, and then its progression. In cardiovascular medicine, many large clinical trials—including the long-running Framingham Heart Study—have identified multiple risk factors predictive of major cardiovascular events such as acute myocardial infarction. Similarly, numerous glaucoma clinical trials have identified risk factors for both the development and progression of glaucoma. These risk factors—such as blood pressure and lipid status in cardiovascular disease and IOP in glaucoma—are both quantifiable and modifiable. In both conditions, therapies that favorably modify risk factors also lower the risk of poor disease outcomes.

Total cholesterol was identified early on as a risk factor for cardiovascular events (Figure 14).<sup>40</sup>

Total cholesterol is analogous to IOP in several important ways. First, like IOP, total cholesterol is a continuous variable. The risk of cardiovascular disease increases incrementally with increasing total cholesterol levels, just as the risk of glaucoma increases with increasing IOP levels.<sup>1</sup> Second, lowering total cholesterol reduces cardiovascular risk, just as lowering IOP reduces glaucoma risk.<sup>9,41</sup> Third, it is challenging to define the limits of “normal” and “abnormal” total cholesterol levels because cardiovascular disease can occur in people across the entire measurable range of total cholesterol—people with normal total cholesterol can still have heart attacks, just as people with normal IOP can still have glaucoma (Figure 15). As with IOP, it is difficult to determine an optimal total cholesterol level.



which are added to determine individual global risk that can then be compared with the average risk of a person of the same age as a benchmark (Figure 18).

In the example in Figures 17 and 18, a 47-year-old smoker with elevated total cholesterol, relatively low HDL cholesterol, and moderately elevated but untreated blood pressure, has a 25% chance of having a heart attack in the next 10 years. In contrast, an average 47-year-old has only a 10% risk of having a heart attack in the same period of time. The patient in the example has a risk that is 2 times higher than average of having a heart attack. This information can assist the physician and patient in developing an appropriate and cost-effective treatment regimen that takes global risk into account

This multivariate approach to global risk assessment can be useful in guiding the intensity of treatment. For instance, the expert panel responsible for cardiology treatment recommendations suggested in 2001 that LDL-cholesterol treatment targets should be set based on global risk assessment (Figure 19).

Patients with a 10-year heart attack risk of less than 10% should aim for an LDL cholesterol level of <160 mg/dL, while patients with a 10-year risk exceeding 20% should be treated more aggressively to lower LDL cholesterol to below 100 mg/dL.<sup>45</sup>

How effectively are the cardiovascular consensus panel's recommendations incorporated into routine clinical practice? Unfortunately, not very well. The general medicine community has demonstrated poor adherence to the cardiovascular treatment guidelines. Fewer than half of patients who would benefit from treatment (eg, blood pressure or lipid reduction, smoking cessation, etc) actually undergo treatment,

2001 ATP III Guidelines			
Risk Category	Risk Factor Profile	Total Risk (10-Year CVD)	Treatment Goal (mg/dL LDL-C)
High	CHD risk (or equivalent)	>20%	<100
Intermediate	≥2 risk factors	10%-20%	<130
		<10%	<130
Low	≤1 risk factor	<10%*	<160

Figure 19. Multivariate risk assessment helped guide intensity of treatment. Expert Panel. NCEP-ATP-III; 2002. NIH publication 02-5215; Grundy. *Am J Cardiol.* 2001;88:23J-27J. ATP=adult treatment panel. \*Most people with ≤1 risk factor have a 10-year risk <10%.

and only about one third of those who are treated actually attain the recommended treatment goals. As many as 40% of patients who seek medical care aren't offered lipid panels to assess their cardiovascular risk. Perhaps most distressing, only about 20% to 25% of patients with established cardiovascular disease—the patients at highest risk—are on treatments to achieve the recommended risk-lowering goals.<sup>46</sup>

This poor adherence to recommendations is comparable to similar observations in glauco-

ma management.<sup>47</sup> Physicians' failure to order lipid panels as part of cardiovascular risk assessment is analogous to ophthalmologists' failure to routinely document the status of the optic nerve and visual field in glaucoma. Similarly, patient noncompliance with IOP-lowering therapy is not uncommon. These noncompliant behaviors on the parts of both patients and caregivers prevent patients from benefiting from available risk-reducing therapies. The successful implementation of global risk assessment in glaucoma will necessitate overcoming the known barriers to compliance.

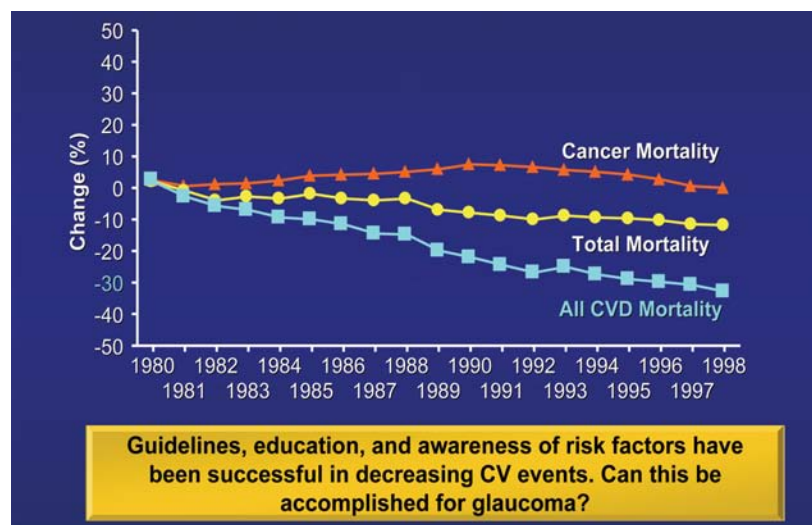


Figure 20. Resulting change in age-adjusted mortality in the United States by cause. From the CDC and Prevention Mortality database. Adapted from Sobel et al. *Circulation.* 2003;107:636-642.

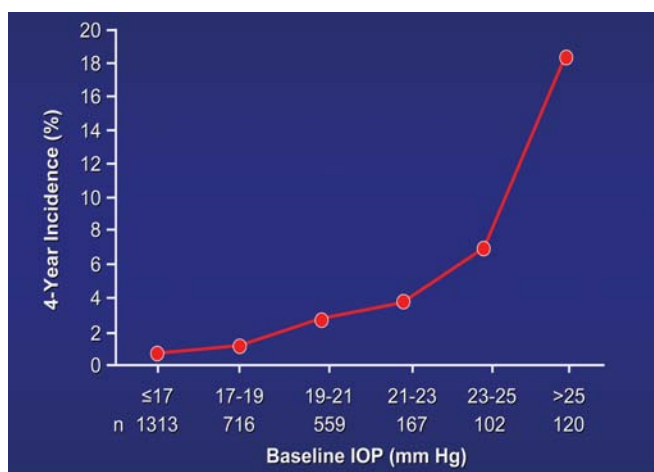


Figure 21. Relationship between increasing IOP and incidence of OAG. Adapted from Leske et al. *Arch Ophthalmol.* 2002;120:954-959.

Despite the incomplete adoption of the cardiovascular risk reduction guidelines, overall cardiovascular mortality has been measurably reduced since the first guidelines were promulgated (Figure 20).

In the last 25 years, death due to cardiovascular disease has dropped 30%.<sup>48</sup> Sadly, this has not reduced overall mortality, as cardiovascular medicine's gains have been erased by a slow but steady rise in cancer death.

Global risk assessment in glaucoma is evolving.

The advances in cardiology are decades ahead of those made in ophthalmology, and have demonstrated that estimating lifelong risk requires lifelong studies. In the interim, while collecting long-term data from ongoing and future clinical trials, the field of ophthalmology needs to fill in some of the gaps in earlier models with reasonable assumptions, just as cardiology did in its early days. A risk model for glaucoma will evolve as more data emerge, and in time it will be possible to determine an individual's risk of developing visual impairment from glaucoma.

## Assessing Glaucoma Risk Factors and Their Effect on Disease Progression

### Key points

- Not every ocular hypertensive patient will develop glaucoma.
- Risk factors for progression from OHT to glaucoma are known.
- Lowering IOP lowers the risk of glaucoma.
- Global risk assessment may help identify the ocular hypertensive patients who are most likely to benefit from risk-lowering treatment.

Risk factors for the development of glaucoma and for the progression of established glaucoma have been identified in recent major clinical trials (refer to Appendix I for a summary of these trials). Global risk assessment based on risk factor analysis represents an evidence-based method to estimate an individual's risk of developing glaucoma and its progression, facilitating an individualized approach to treatment.

The most significant risk factor for the development or progression of glaucoma is IOP. The Barbados Incidence Study of Eye Diseases demonstrated a dramatic incremental increase in glaucoma risk with increasing IOP (Figure 21). Eyes with IOP above 25 mm Hg were 25 times more likely to develop glaucoma than eyes with IOP of 17 mm Hg.<sup>49</sup>

But IOP is not the only risk factor for glaucoma and its progression. OHTS identified several risk factors predictive for the development of glaucoma in eyes with elevated IOP (Figure 22).<sup>50</sup>

Similarly, the Early Manifest Glaucoma Trial (EMGT) identified numerous risk factors predictive for progression in eyes with established glaucoma (Figure 23).<sup>29</sup> Some risk factors such as age, IOP, and visual field status, are predictive for both the development and the progression of glaucoma.

Risk Factor	For Every...	Estimated Risk for Glaucoma Increased...
Age	10 year ↑	22%
IOP	1 mm Hg ↑	10%
CCT	40 μm ↓	71%
Horizontal C/D ratio	0.1 ↑	27%
Vertical C/D ratio	0.1 ↑	32%
Standard pattern deviation	0.2 dB ↑	27%

Figure 22. Baseline risk factors for progression from OHT to glaucoma (OHTS). Adapted from Gordon et al. *Arch Ophthalmol.* 2002;120:714-720. CCT=central corneal thickness; C/D=cup/disc.

Risk Factor	Estimated Risk for Glaucoma Progression Increased
Age ( $\geq 68$ years)	47%
IOP ( $\geq 21$ mm Hg)	70%
PSD ( $\geq 4$ )	58%
Exfoliation syndrome	122%
Bilateral VF loss	96%

Figure 23. Risk for progression of established glaucoma. Leske et al. *Arch Ophthalmol.* 2003;121:48-56. PSD=pattern standard deviation.

Translating these identified risk factors into a clinically useful model to guide therapy decisions is a multistep process.<sup>10</sup> First, reasonable population estimates of progression from OHT to blindness must be determined. From these population-based estimates, thresholds for low, moderate, and high risk with accompanying treatment recommendations based on risk level are then established. Finally, a quantitative estimate of a patient's risk of developing glaucoma or its progression based on the patient's individual risk factors is made. This patient's risk can then be categorized as low, medium, or high, and guidelines for each level will provide treatment recommendations based on global risk assessment.

In order to accomplish the first step (estimating the global risk of progressing from OHT to blindness from existing data), several assumptions must be made.<sup>10</sup> First, progression is assumed to be linear over time. This assumes that an individual's risk of progressing from OHT to glaucoma or glaucoma to blindness does not change depending on how long the individual has had OHT or glaucoma. This may not be an accurate assumption; someone with OHT for 25 years has demonstrated resilience to elevated IOP exposure and may be at lower risk of progression to glaucoma than someone with OHT for

only 2 or 3 years. A second assumption is that the risk of progressing from OHT to glaucoma is independent of the risk of progressing from established glaucoma to blindness. This assumption is necessary because the best data available are from studies of either progression from OHT to glaucoma, or of progression from glaucoma to blindness, with almost no studies including both of these phases of progression. In essence, the risk estimate for the overall progression from OHT to blindness will be developed by combining the individual risks of these 2 tandem events (OHT to glaucoma and glaucoma to blindness). Because of this necessary approach, the third assumption is that end points of studies estimating the risk of progression from OHT to glaucoma are equivalent to the entry criteria for studies estimating the risk of progressing from glaucoma to blindness (ie, that patients developing glaucoma in the former studies would immediately be eligible to participate in the latter studies). This assumption ensures that the entire span of disease is described by existing data. Finally, blind-

ness is defined as blindness in one or both eyes as defined by visual field criteria described in the Advanced Glaucoma Intervention Study (AGIS)<sup>51</sup> and Collaborative Initial Glaucoma Treatment Study (CIGTS)<sup>52</sup> studies.

With these assumptions in place, several trials provide the necessary data to construct an estimate of the global risk of progressing from OHT to blindness. The first is the OHTS, which reported the risk of progressing from OHT to early manifest glaucoma.<sup>41</sup> The 2 others are the St. Lucia<sup>53</sup> and Olmsted County<sup>54</sup> population-based studies providing estimates of the risk of progressing from glaucoma to blindness. The St. Lucia study has 2 important limitations. First, its subjects were exclusively Afro-Caribbean. This is important because glaucoma is both more common and more aggressive in black populations, so that the data from this study may not be completely generalizable to a Caucasian population. Second, because St. Lucia is a poor nation without a subsidized healthcare system, very few patients diagnosed with glaucoma in St. Lucia received treatment during the study period. While this permits assessment of the natural history of untreated glaucoma, it provides no insight into potential benefits of treatment. The Olmsted County, Minnesota, study also has limitations. Among

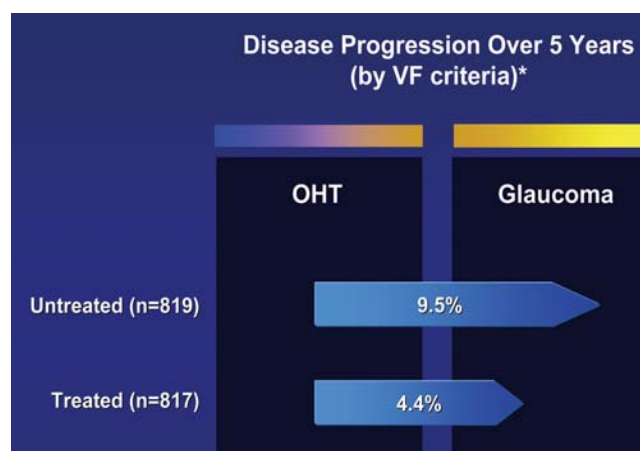


Figure 24. Reported progression rates. OHTS (N=1636). Kass et al. *Arch Ophthalmol.* 2002;120:701-713.

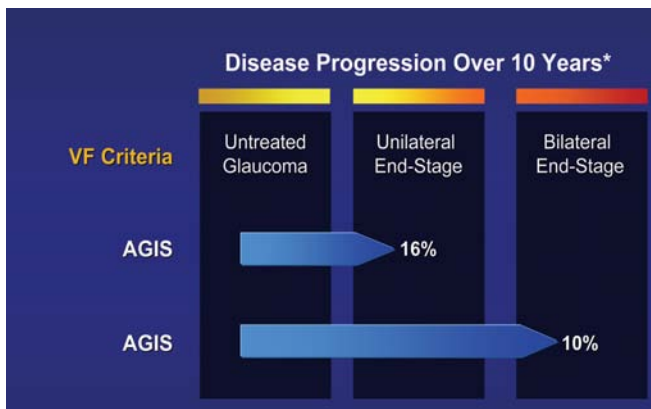


Figure 25. Reported progression rates. St. Lucia Study Cohort (N=205). Wilson. *Trans Am Ophthalmol Soc.* 2002;100:365-410; Wilson et al. *Am J Ophthalmol.* 2002;134:399-405. \*10-year cumulative probability based on 146 right eyes and 141 left eyes.

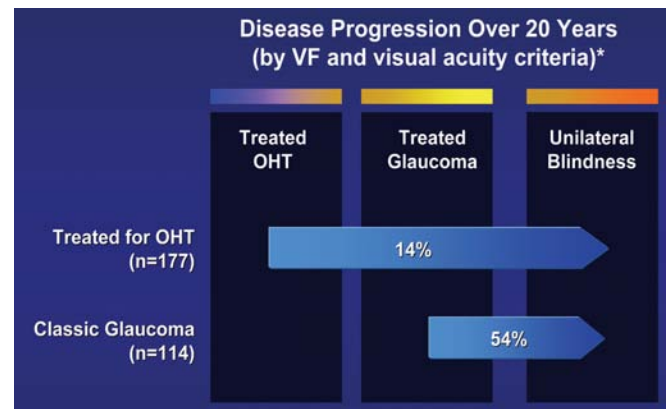


Figure 26. Reported progression rates. Olmsted County Study Cohort (N=295). Hattenhauer et al. *Ophthalmology.* 1998;105:2099-2104. \*Cumulative 20-year progression.

these is its retrospective nature, which precluded any standardization of examination findings or follow-up schedules. In addition, the study was relatively small. Although 295 patients were included in the analysis, fewer than half had follow-up exceeding 15 years, and only 67 were followed up for 20 or more years. Because the EMGT did not have blindness as an end point, its findings cannot be applied in the model.<sup>9</sup>

From the OHTS, the global 5-year risk of progressing from OHT to glaucoma, for both treated and untreated patients, is 4.4% and 9.5%, respectively (Figure 24).<sup>41</sup>

From the St. Lucia study, the global risk of progressing from glaucoma to unilateral and bilateral blindness in untreated patients is 10% to 16% over 10 years (Figure 25).<sup>53</sup>

The Olmsted County study provides a 20-year estimate of the risk of progressing from established glaucoma to unilateral blindness of 54% (Figure 26).<sup>54</sup>

To estimate the global 15-year risk of progressing from OHT to blindness in untreated eyes, prior assumptions permit multiplying the risks of the 2 intermediate steps: progression from OHT to glaucoma, and glauco-

ma to blindness (Figure 27).<sup>10</sup>

Specifically, the 5-year risk of progressing from OHT to glaucoma from OHTS, 9.5%, multiplied by the 10-year risk of progressing from glaucoma to blindness from St. Lucia (using the worst-case AGIS criteria), 16%, yields a total 15-year risk of an untreated ocular hypertensive patient progressing to unilateral blindness of 1.5% (Figure 28).

Alternatively, using the Olmsted County data, multiplying the 5-year OHTS risk, 9.5%, by the 10-year risk of progressing from glaucoma to unilateral blindness reported in the

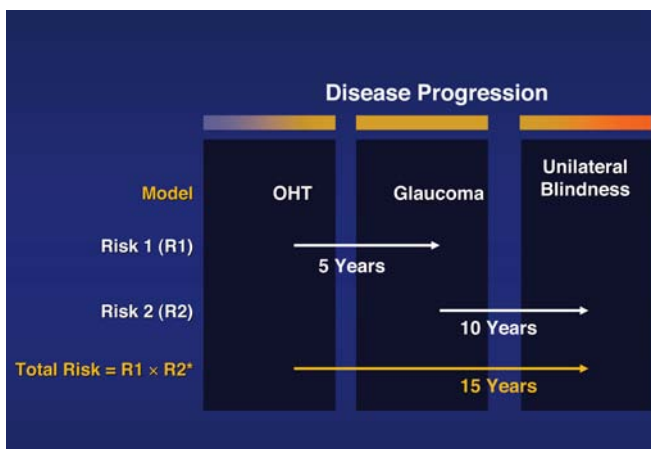


Figure 27. Model assumptions. Wilson et al. *Am J Ophthalmol.* 2002;134:399-405. Wilson. *Trans Am Ophthalmol Soc.* 2002;100:365-410.

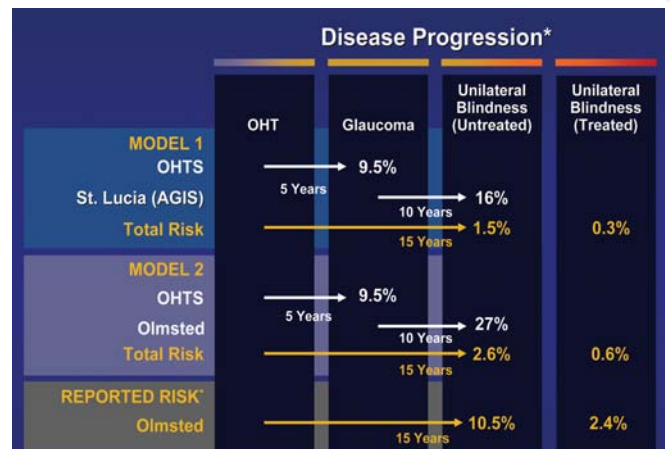


Figure 28. Reported progression rates. Treated patients with OHT. Weinreb et al. *Am J Ophthalmol.* 2004;138:458-467. \*Cumulative 15-year progression.



Figure 29. Impact of treatment on risk. Kass et al. *Arch Ophthalmol.* 2002;120:701-713; Leske et al. *Arch Ophthalmol.* 2003;121:48-56.

Olmsted County study (halving their reported 20-year risk of 54%), 27%, yields a remarkably similar 15-year risk of an untreated ocular hypertensive patient progressing to unilateral blindness of 2.6% (Figure 28).

As a measure of validation for this model, these estimates compare favorably with the 15-year risk of progressing from OHT to unilateral blindness reported in the Olmsted County study of 10.5% (Figure 28).<sup>54</sup>

These global risk estimates are for untreated eyes. Applying the same assumptions, the estimated potential benefit of treatment, from the OHTS and EMGT, is a net 75% risk reduction of progressing from OHT to blindness (Figure 29).<sup>9,41</sup>

Applying this treatment-related risk reduction to the global risk estimates, the 15-year risk of progressing from OHT to blindness is reduced to approximately 0.3% to 0.6% with treatment (Figure 28, last column).<sup>10</sup>

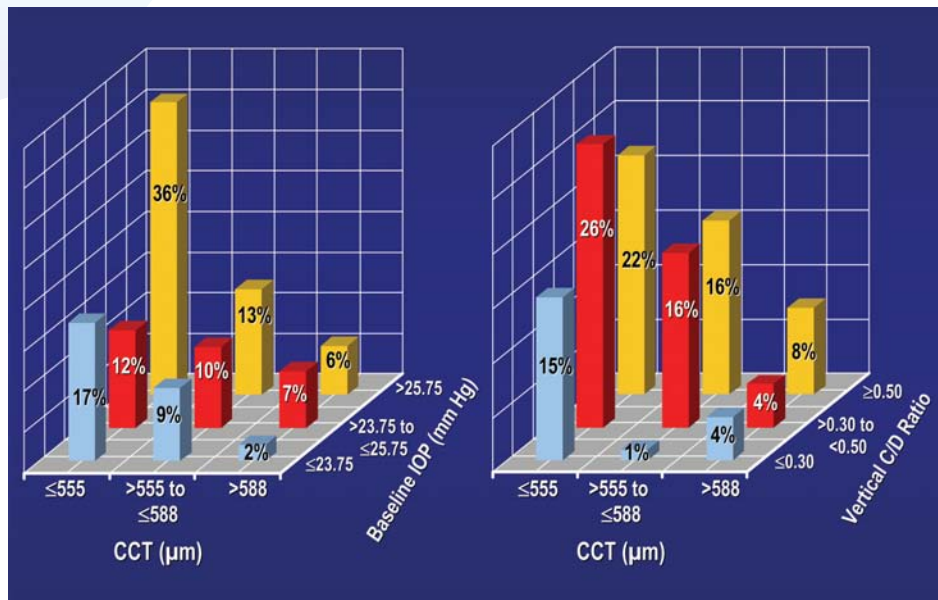


Figure 30. OHTS 3-by-3 tables of risk. Gordon et al. *Arch Ophthalmol.* 2002;120:714-720.

The numbers in Figure 26 represent the population average risk of progressing from OHT to blindness. They do not provide information on individual risk, but serve as the benchmark against which individual risk can be compared—much as individual cardiovascular risk is compared to age-matched population averages (refer to Figure 18). Estimating an individual's global risk of progressing from OHT to blindness requires a multivariate risk calculator similar to the Framingham cardiovascular risk calculator.

### Integrating Risk Assessment Into Patient Care

#### Key points

- A validated tool for estimating risk of progression from OHT to glaucoma based on individual risk factors has been developed.
- Risk thresholds and corresponding treatment guidelines have been proposed.
- Moderate- and high-risk patients can be identified and treated to lower their risk of glaucoma-related vision loss.

Every time treatment is considered for a patient with OHT, a global risk assessment is performed. Often, this process is a qualitative analysis based on the number and severity of risk factors the patient has. With its now-familiar 3-by-3 tables of risk stratified by IOP, central corneal thickness, and vertical cup–disc ratio, the OHTS study moved risk analysis toward a semiquantitative assessment (Figure 30).<sup>50</sup>

Although there were earlier attempts to develop risk calculators for glaucoma, the first quantitative and validated individualized glaucoma risk calculator debuted in October 2005. It was modeled on risk calculators developed earlier for the Framingham Heart Study. Based upon the risk factors identified in the OHTS, this glaucoma risk calculator permits clinicians to derive a 5-year probabil-

Step 1		Step 3		Step 4		Step 6	
Age, y	Points	CCT, $\mu\text{m}$	Points	Vertical C/D Ratio	Points	DM	Points
40-44	0	450-469	30	0.1	0	Yes	-9
45-49	1	470-489	27	0.2	2	No	0
50-54	2	490-509	24	0.3	5		
55-59	3	510-529	21	0.4	7		
60-64	4	530-549	19	0.5	10		
65-69	5	550-569	16	0.6	12		
70-74	6	570-589	13	0.7	15		
75-80	7	590-609	11	0.8	17		
		610-629	8	0.9	20		
		630-649	5				
		650-669	3				
		670-689	0				

Step 2		Step 5		Step 7	
IOP, mm Hg	Points	PSD	Points	Total Points	5-Year Risk, %
23	0	1.00-1.19	0	-9-12	<1
24	1	1.20-1.39	2	13-27	1-5
25	2	1.40-1.59	4	28-33	6-10
26	3	1.60-1.79	6	34-37	11-15
27	4	1.80-1.99	8	38-40	16-20
28	5	2.00-2.19	10	41-44	21-30
29	6	2.20-2.39	12	45-47	31-40
30	7	2.40-2.59	14	48-50	41-50
31	7			>50	>50
32	8				

Figure 31. Point system to calculate the risk of glaucoma development in 5 years. Medeiros, Weinreb, et al. *Arch Ophthalmol.* 2005;123:1351-1360.

“The idea for a risk calculator for estimating the risk of an ocular hypertensive patient developing glaucoma evolved through discussions with the investigators of the Framingham Heart Study.”

– Robert N. Weinreb, MD

an individual patient’s value for each risk factor. The 6 risk factor scores are added for an overall risk score, which is then converted to a 5-year predicted risk for glaucoma development.

For instance, consider a typical 62-year-old woman with elevated IOP but normal optic nerves and SAP. She earns 4 points for age alone. Her untreated IOP is 25 in both eyes

ity estimate that a particular ocular hypertensive patient will progress to glaucoma based on their own risk-factor profile.<sup>55</sup>

The OHTS-derived risk estimation model considers 6 key risk factors: age, IOP, pattern standard deviation on SAP, central corneal thickness, vertical cup–disc ratio, and diabetes status. In the model, each of these is weighted according to its predictive power for identifying the ocular hypertensive patients likely to progress to glaucoma. To ensure that the OHTS findings are typical of ocular hypertensive patients—and that its findings can be general-

ized to other populations—each risk factor’s weight was independently verified in a second, independent database of ocular hypertensive patients. This was accomplished using data from the National Eye Institute–sponsored Diagnostic Innovations in Glaucoma Study (DIGS), involving an independent sample of ocular hypertensive patients followed longitudinally at the Hamilton Glaucoma Center, University of California, San Diego. All risk factors except diabetes status were found to be comparably predictive of glaucoma conversion risk in both the OHTS and Hamilton Glaucoma Center data sets; the predictive power of diabetes was protective against glaucoma in the OHTS and not protective in the DIGS patients.

Once validated, the mathematically cumbersome equation for calculating risk estimates was reduced to a more user-friendly point system (which was then validated against the original equation and found to have near-perfect agreement). The point system (Figure 31) awards points for each risk factor based on

“OHTS found that diabetes was protective of glaucoma. We do not reach the same conclusion for the ocular hypertensive patients enrolled in the DIGS.”

– Robert N. Weinreb, MD

(2 points). She has average corneas, in the range of 550 microns (16 points). Her vertical cup–disc ratio is only 0.2 (2 points), her standard achromatic field gave a pattern standard deviation of 1.5 (4 points), and she is not diabetic (0 points). Her overall risk score is the sum of her individual risk scores (in this case, 4 + 2 + 16 + 2 + 4 + 0 = 28), which converts to a predicted 5-year risk of developing glaucoma of 6% to 10%.

Once the risk calculator has estimated an individual’s global risk of progressing from OHT to glaucoma, the clinician and patient have a valuable piece of information upon

“The 3-by-3 risk tables from OHTS were not useful because they only provided limited information about the plethora of risk factors and did not include estimates of their interaction.”

– Robert N. Weinreb, MD

Risk Level	Range	Recommendations
Low	<5%	Monitor
Moderate	5%-15%	Consider treatment
High	>15%	Treatment

**Treatment strategies should focus on moderate- and higher-risk patients**

Figure 32. Risk thresholds to guide patient management: 5-year risk for conversion of OHT to glaucoma. Weinreb et al. *Am J Ophthalmol.* 2004;138:458-467.

which to base their management. But the global risk estimate provided by the risk calculator does not directly address whether or not to treat an individual patient; the risk calculator simply provides a number between 0 and 100 that represents the individual's risk of developing glaucoma within 5 years.

**“Baseline intraocular pressure for the risk calculator was the average of the 2 eyes over 2 consecutive visits.”**

– Robert N. Weinreb, MD

This estimate provides useful information that can assist clinicians in deciding which ocular hypertensive patients should be treated, and which should not be treated. In the example above, is a 5-year risk of 6% to 10% worthy of treatment to lower this risk or not?

To help guide clinicians and patients in the use of these risk estimates, an expert panel of 11 glaucoma specialists met over a 2-year period to develop consensus recommendations for treatment based on the estimates provided by the risk calculator compared with the known benchmark population risk estimates discussed above. In developing these

guidelines, the panel reviewed the existing glaucoma literature from 1966 to the present. Recognizing the parallels between glaucoma and cardiovascular medicine—and the progress cardiology has made in developing tools for individual risk assessment—the panel met with some of the original architects of the Framingham Heart Study and its risk calculator, gleaned valuable insights from experts familiar with the risk-assessment roadmap. After creating the models discussed above to estimate population and individual risks of glaucoma blindness, the panel developed the following treatment recommendations based on individual 5-year risk of progressing from OHT to glaucoma (Figure 32).<sup>10</sup>

An ocular hypertensive patient whose individual risk of developing glaucoma within 5 years is less than 5%—as determined by the risk calculator based on that individual's personal risk factor profile—can be safely observed without treatment. These low-risk patients should undergo regular examinations of the optic nerve and peripapillary NFL, as well as perimetry, as part of their monitoring. The clinician should ensure that baseline data, including documentation of the optic nerve's appearance, are of high quality and will permit future serial comparisons. These individuals should

**“I once thought that younger ocular hypertensive patients, being healthier, had a lower risk of developing glaucoma in their lifetime. But now I realize that risk compounds over time. A young person may have a significant lifetime risk even if their baseline 5-year risk is low.”**

– Robert N. Weinreb, MD

also undergo periodic reassessment of risk factor status, as low-risk patients can occasionally become high-risk patients if key risk factors change over time. The clinician must ensure that these patients understand the importance of regular follow-up to detect asymptomatic progression.

Patients whose 5-year risk of progressing to glaucoma is between 5% and 15% are at higher risk if untreated than if treated, but the benefits of treatment are only moderate. In these individuals, treatment may or may not be appropriate, based in part on the comfort thresholds of the patient and physician after a discussion of the risks of treating versus not

**“This risk calculator tool should be considered an adjunct to—not a substitute for—our own clinical judgment and experience.”**

– Robert N. Weinreb, MD

treating. Keeping in mind that the risk calculator provides 5-year risk, not lifetime risk, younger patients may be at greater lifetime risk of developing glaucoma, and treatment of these patients should be seriously considered. Monitoring of structure and function in these patients is as important as in low-risk patients, and should perhaps be more frequent in patients who opt not to be treated compared with those who opt for treatment.

Patients whose individual risk of progressing from OHT to glaucoma within 5 years exceeds 15% are at high risk.<sup>41</sup> High-quality baseline testing of structure and function are key to identifying potential for subsequent progression. These patients are most likely to benefit from treatment, and clinicians should make every effort to ensure that the patients understand this benefit and accept treatment. Therapeutic targets should be set and discussed with the patient to ensure his/her active participation in meeting these goals.

**“The risk calculator is not solely about treating patients, but it is also about identifying those patients who have a low risk for progression and do not need treatment. It’s about allocating our resources and targeting treatment for patients with moderate or high probability of developing disease to increase the benefit–risk ratio of therapy.”**

– Robert N. Weinreb, MD

Also, patients must understand that treatment reduces, but does not eliminate, risk, and that regular follow-up will still be required to continually assess the efficacy of therapy.

The glaucoma risk calculator is a useful tool for clinicians in estimating an individual patient’s risk of developing glaucoma, but it is not meant to replace the clinician’s own experience and judgment. Similarly, the consensus risk thresholds and treatment recommendations described above are meant to serve as a guide for clinicians who may have their own thresholds for offering treatment to ocular hypertensive patients. Several important clinical factors not included in the risk calculator may also play a role in deciding whether or not

**“Perhaps a future risk calculator will incorporate life expectancy. These data are out there—actuarial tables exist.”**

– Robert D. Fechtner, MD

to offer treatment. Among these is life expectancy. Older ocular hypertensive patients—and some younger patients in poor health—may not be expected to live long enough to develop glaucoma and subsequently become blind from it, and may not warrant treatment. Alternatively, older patients with a family history of longevity may warrant treatment. Another important determinant of whether or not to treat is patient preference. Some patients are more risk averse than others; some may be more averse to the risks of treatment than the risks of vision loss.

Several important limitations of the glaucoma risk calculator exist. It is not known whether the tool can be used in ocular hypertensive eyes that have clinical characteristics that differ from the entry criteria for the OHTS study. This includes eyes with an untreated IOP of less than 23 mm Hg or more than 32 mm Hg, or patients younger than age 40 or older than age 80. It cannot be applied to eyes already receiving IOP-lowering treatment, nor can a risk reduction be inferred by applying the calculator before and after treatment. Also, the tool provides no information on the risk of progression in eyes with established glaucoma.

Global risk assessment for glaucoma is evolving. Patients present in all stages of the glaucoma continuum. Clinicians are challenged to identify those patients whose risk of glaucoma-related vision loss justifies treatment. The glaucoma risk calculator, as an adjunct to clinical experience, may assist clinicians in identifying those patients with OHT who are most at risk for glaucoma-related vision loss.

## Conclusion

Two questions were presented at the beginning of this monograph. It is useful now to revisit them.

Can the ocular hypertensive patients at greatest risk for glaucoma-related visual impairment be identified? The answer is yes. As major clinical trials have identified risk factors for the development and progression of glaucoma, the ability to assess global risk has evolved from qualitative estimates to semi-quantitative analysis to robust global risk assessment using the new OHTS-derived and DIGS-validated glaucoma risk calculator.<sup>55</sup>

What implications would this risk assessment have for individualized treatment recommendations? Clearly, it is inappropriate to treat all ocular hypertensive patients, and it is equally inappropriate not to treat any ocular hypertensive patients. Knowing an individual patient’s risk of developing glaucoma compared with population-based risk estimates permits treatment of patients at risk. Global risk assessment helps clinicians quantitatively measure an individual ocular hypertensive patient’s risk for developing glaucoma. Once identified, physicians and patients together can determine whether risk reduction therapy is appropriate on an individual basis.

As in cardiology, the glaucoma risk calculator will evolve as new data emerge from ongoing and future clinical trials. Risk estimates will grow more accurate as more is learned about glaucoma risk factors and their relative predictive power. As global risk assessment is incorporated into clinical care and at-risk patients are appropriately treated, it is expected that the incidence of glaucoma-related vision loss will be reduced.

# APPENDIX I

## A Reference Guide to Major Glaucoma Clinical Trials

### Ocular Hypertension Treatment Study

This prospective trial randomized patients with OHT (with normal visual fields and optic nerves) either to observation (no treatment) or to treatment (the goal being a 20% IOP reduction) to determine if lowering IOP prevents progression to glaucoma. After 5 years, 9.5% of untreated patients versus only 4.4% of treated patients developed glaucomatous visual field loss or optic nerve changes. Baseline risk factors associated with higher risk of progression to glaucoma included thinner central corneas, higher IOP, and older age.

### Early Manifest Glaucoma Trial

This prospective trial, conducted in Sweden, randomized patients with confirmed open-angle glaucoma (including normal-tension glaucoma and pseudoexfoliation glaucoma) either to observation (no treatment) or treatment with argon laser trabeculoplasty (360 degrees) and betaxolol twice daily (but no predefined IOP goals) to determine if lowering IOP prevents progression of manifest glaucoma. After 6 years, 62% of untreated patients versus 45% of treated patients developed progressive optic nerve or visual field changes. Baseline risk factors associated with higher risk of progression included higher IOP, pseudoexfoliation, greater visual field loss, and older age.

### St. Lucia Study

This population-based epidemiologic survey, conducted from 1986 to 1987, consisted of a screening eye examination in almost 1700 Afro-Caribbean residents of St. Lucia, a small Caribbean island, to determine the prevalence of glaucoma. The original study reported an 8.8% prevalence of glaucoma in this population. Because of economic limitations, the vast majority of identified glaucoma patients did not receive treatment. In 1997, the glaucoma patients were re-examined to determine the natural progression of untreated open-angle glaucoma. In the intervening 10 years, 55% of patients had experienced visual field loss progression, and 16% had progressed to end-stage based on AGIS visual field grading criteria.

### Olmsted County Study

This population-based, retrospective study examined the prevalence of blindness among predominantly Caucasian residents of Olmsted County, Minnesota, who were diagnosed with glaucoma from 1965 to 1980. Using the standard definition of legal blindness (acuity of 20/200 or worse in the better eye or visual field constriction to 20 degrees or less), this study reported a 20-year prevalence of glaucoma-related blindness of 27% in one eye and 9% in both eyes.

### Barbados Incidence Study of Eye Diseases

This longitudinal, population-based epidemiologic survey, conducted from 1988 to 1992, consisted of a baseline screening eye examination and a follow-up examination 4 years later to determine the incidence of open-angle glaucoma in this predominantly Afro-Caribbean population. This study reported that the 4-year incidence of glaucoma varied markedly with baseline IOP (Figure 21).

### Baltimore Eye Study

This population-based prevalence study—conducted in Baltimore, Maryland, in the 1980s—consisted of a screening of more than 5000 residents aged 40 years or older, approximately half of whom were African American and half were Caucasian. This study found the prevalence of open-angle glaucoma varied markedly with baseline IOP (Figure 3).

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# Posttest Questions

**1. What is the projected prevalence of POAG in America by 2020?**

- a. 1.6 million
- b. 2.2 million
- c. 3.4 million
- d. 5.1 million

**2. Approximately how many patients are unaware that they have glaucoma?**

- a. 10%
- b. 25%
- c. 50%
- d. 85%

**3. What is the correct order of progression?**

- a. OHT → Glaucoma → Functional Impairment → Blindness
- b. OHT → Functional Impairment → Glaucoma → Blindness
- c. Glaucoma → OHT → Functional Impairment → Blindness
- d. Functional Impairment → OHT → Glaucoma → Blindness

**4. At which stage in the continuum does retinal nerve fiber loss start?**

- a. Undetectable
- b. Asymptomatic
- c. Functional impairment
- d. Blindness

**5. Which of these techniques does not assess the optic nerve?**

- a. Confocal scanning laser ophthalmoscopy
- b. Short-wavelength automated perimetry
- c. Scanning laser polarimetry
- d. Stereophotography

**6. Stereophotography is still a useful way to record and maintain a permanent record of the optic disc.**

- a. True
- b. False

**7. Which of these is not true of confocal scanning laser ophthalmoscopy?**

- a. Assesses optic disc topography
- b. Provides measure of optic disc size
- c. Can predict the development of visual field loss
- d. Never requires pupillary dilation

**8. The patient always develops detectable optic nerve damage before standard automated perimetry damage occurs.**

- a. True
- b. False

**9. Standard automated perimetry may detect VF changes earlier than short-wavelength automated perimetry.**

- a. Always
- b. Sometimes, but rarely
- c. Never

**10. Which of the following is not a similarity between CVD and glaucoma?**

- a. They are both chronic diseases
- b. They both have a risk calculator available
- c. There are clinical trials on risk
- d. They both have many modifiable risk factors

**11. What have we learned from CHD global risk?**

- a. Global risk assessment improves management decisions and health care
- b. Global risk assessment can be based on short-term studies
- c. Assumptions should be made later in the process
- d. Limited evidence is sufficient to develop a risk model

**12. Which of these is not a risk factor for developing OAG?**

- a. IOP
- b. Sex
- c. Race
- d. CCT

**13. What did OHTS find to be the reduction in risk of progression over 5 years by treating patients?**

- a. 10%
- b. 30%
- c. 50%
- d. 75%

**14. Why is risk factor assessment important?**

- a. Applies evidence-based medicine to clinical care
- b. Improves individualization of care
- c. Estimates an individual's rate of progression
- d. All of the above

**15. An OHT risk calculator**

- 1. Identifies patients at high and low risk for glaucoma development
  - 2. Assists in decisions about the monitoring and treatment of a patient suspect of glaucoma
  - 3. Determines the rate of progression to blindness in previously diagnosed glaucoma patients
- a. 1
  - b. 1 and 2
  - c. 1 and 3
  - d. 1, 2, and 3

**16. The validated risk model for OHT assesses the risk of glaucoma development over how many years?**

- a. 1 year
- b. 2 years
- c. 5 years
- d. 10 years

**17. What percentage range is considered to be a moderate risk of glaucoma development?**

- a. 0% to 5%
- b. 5% to 15%
- c. 10% to 20%
- d. 25% to 30%

**18. Is the presence of a moderate/high risk of developing glaucoma sufficient to indicate treatment?**

- a. Yes
- b. No
- c. Unknown

**19. What needs to be considered when assessing the risk of glaucoma in younger patients?**

- a. They have lower risk than older patients
- b. They have a greater cumulative risk of vision loss over their lifetime
- c. They have a lower cumulative risk of vision loss over their lifetime
- d. They do not need treatment

**20. Using figure 31 as a guide on how to use the risk calculator to calculate the 5-year predicted risk of glaucoma, what is the risk of this patient developing glaucoma?**

**Patient 1**

Age, y	.67
IOP, mm Hg	.30
CCT, μm	.527
Vertical C/D ratio	.04
PSD	1.85
DM	.No

- a. 6% to 10%
- b. 16% to 20%
- c. 21% to 30%
- d. 31% to 40%

11. a	10. d
12. b	9. b
13. c	8. b
14. a	7. d
15. b	6. a
16. c	5. b
17. d	4. a
18. c	3. a
19. b	2. c
20. a	1. c

Answer Key

## Activity Evaluation Form

The planning and execution of useful and educationally sound continuing education activities are guided in large part by input from participants. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few moments to complete this evaluation form. Your response will help ensure that future programs are informative and meet the educational needs of all participants. Thank you for your cooperation!

# CME CREDIT

# IS NO LONGER

# AVAILABLE FOR

# THIS ACTIVITY

### PROGRAM OBJECTIVES

Having completed this activity, are you better able to

	5=Strongly agree			1=Strongly disagree	
	5	4	3	2	1
Review the glaucoma continuum	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Explain the concept of global risk as it applies to treatment decisions in glaucoma	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Examine evidence supporting risk calculations	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Determine an appropriate management approach for best clinical outcomes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

### OVERALL EVALUATION

	5=Strongly agree			1=Strongly disagree	
	5	4	3	2	1
The information presented increased my awareness/understanding of the subject.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The information presented will influence how I practice.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The information presented will help me improve patient care.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The program was educationally sound and scientifically balanced.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The program avoided commercial bias or influence.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Overall, the program met my expectations.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I would recommend this program to my colleagues.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide us with a brief description of how you plan to do so.

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Please provide any additional comments pertaining to this activity (positives and negatives) and suggestions for improvement.

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Please list any topics that you would like to be addressed in future educational activities.

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Please return this evaluation form along with your completed Registration Form.

**University of Medicine and Dentistry of New Jersey**

**Center for Continuing & Outreach Education**

*Treatment of Risk in the Glaucoma Continuum*

**Registration Form**

In order to obtain AMA PRA category 1 credit, participants are required to

- (1) Read the learning objectives, review the activity, and complete the self-assessment test
- (2) Complete this registration form and the activity evaluation form and record test answers in the box below.
- (3) Send the registration, self-assessment test, and evaluation forms to:  
Impact Communications  
**via mail:** 330 Madison Avenue, 21st Floor, New York, NY 10017  
**via fax:** (212) 983-3269  
**via online:** www.GlaucomaRisk.com
- (4) If completed online, participants will receive an electronic, printable statement of credit immediately after successfully completing the posttest. If sent via mail or fax, participants will be mailed a statement of credit by UMDNJ within 6 weeks.

**SELF-ASSESSMENT TEST**

Circle the best answer for each question on page 22.

1	a	b	c	d
2	a	b	c	d
3	a	b	c	d
4	a	b	c	d
5	a	b	c	d
6	a	b	c	d
7	a	b	c	d
8	a	b	c	d
9	a	b	c	d
10	a	b	c	d
11	a	b	c	d
12	a	b	c	d
13	a	b	c	d
14	a	b	c	d
15	a	b	c	d
16	a	b	c	d
17	a	b	c	d
18	a	b	c	d
19	a	b	c	d
20	a	b	c	d

CME CREDIT IS NO LONGER AVAILABLE FOR THIS ACTIVITY

**REGISTRATION**

FIRST NAME M.I. LAST NAME DEGREE

DAYTIME PHONE EVENING PHONE

FAX E-MAIL

PREFERRED MAILING ADDRESS ( HOME  BUSINESS)

CITY STATE ZIP CODE

AFFILIATION SPECIALTY

I attest that I have completed the *Treatment of Risk in the Glaucoma Continuum CME-Certified Monograph* activity as designed and I am claiming [up to 2.5 credits] \_\_\_\_\_ AMA/PRA category 1 credits.

CME CREDIT IS NO LONGER AVAILABLE FOR THIS ACTIVITY

SIGNATURE DATE



